IDENTIFYING THE COGNITIVE DECREMENTS CAUSED BY HIV: FINAL REPORT

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This document summarizes the work conducted on this grant. One major experiment was conducted examining the effects of HIV on cognitive processes for a group of asymptomatic HIV+ homosexual and bisexual males, as defined using the Walter Reed Classification System. The HIV+ subjects were compared to a matched group of HIV- homosexual and bisexual males and to a second group of matched HIV- heterosexual males. Two types of cognitive assessment systems were used: information processing and neuropsychological.

A comparison of the two HIV- control groups revealed a number of significant differences on both the information processing and the neuropsychological instruments. Consequently, the group consisting of HIV- homosexual and bisexual males was selected as the appropriate control group. Few differences were found between the control group and the asymptomatic, HIV+ group.

An interesting relation between performance on a classical vigilance task and self-reported recreational drug use was found. These data indicated that vigilance tasks may be useful as non-invasive drug screens.

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OVERVIEW

This is the final report on Contract N00014-90-J-4079, Identifying the Cognitive Deficits Caused by HIV. Three studies were conducted under this contract. The first, which represents the primary product of this contract, was designed to identify the stage of HIV infection at which cognitive deficits first can be identified and to compare the relative sensitivity of neuropsychological instruments and information processing tests. This study produced a number of surprising findings, which led to two subsequent studies and to a number of publications.

This report is divided into four major sections. The first summarizes the goals, methods, and results of the main experiment. This section also describes some of the more surprising findings and the resulting publications. Section 2 describes a brief pretest that was conducted to verify some of the unusual results of the main study. Section 3 describes another study that was conducted to obtain more data on one of the tests used in the main study. The fourth section lists all of the products of this contract. These four sections will be discussed in turn.

MAIN STUDY

Summary

This study is reported in Damos, John, Parker, and Levine (1994). Consequently, only a brief overview will be provided. This study had two primary purposes. The first was to determine the disease stage at which cognitive decrements become detectable in HIV+ individuals. The second was to compare the sensitivity of information processing tests to that of neuropsychological instruments. A secondary purpose concerned assessing the appropriateness of various control groups. Most studies of cognitive processes limit the HIV+ group to homosexual or bisexual males who contracted the disease sexually. However, the composition of the control groups has varied considerably in these studies. In many studies, the control group consists of homosexual and bisexual males. In some cases it apparently has consisted of homosexual, bisexual, and heterosexual males (e.g., Poutiainen et al., 1993). In a few cases, women have been included in the control group (Karlsen et al., 1992). Such control groups may not be comparable to the HIV+ groups on a variety of lifestyle factors that may affect performance on both neuropsychological and information processing instruments. Inappropriate control groups, therefore, may lead to a misinterpretation of observed performance differences.

Subjects were recruited into five groups. Three groups consisted of HIV+, homosexual or bisexual males. The first group was composed of asymptomatic HIV+ males in Walter Reed Stages 1, 2, and 3. The second group consisted of symptomatic HIV+ males in Walter Reed Stages 4 and 5. The third group consisted of HIV+ males who were taking AZT, DDI, DDC, or any combination of these drugs. The design also included two control groups of HIV- males. The fourth group consisted of homosexual or bisexual males; the fifth group, of heterosexual males. The five groups were matched on the mean, range, and distribution of scores for age and education. The proportion of minorities in each group was kept approximately equal.

Candidates completed a 20 to 25 min screening interview to determine their eligibility for participation. The inclusion criteria were: age between 21 and 50 years, at least 12 years of formal education (including the receipt of a high school diploma), and English as the native language or acquired by age 6. The exclusion criteria included a self-reported history of: treatment for alcoholism or drug abuse, head injury or other episodes with a loss of consciousness greater than 5 min, convulsions or seizures, treatment for severe mood swings or other psychotic disorders, stroke, brain tumor, cancer (other than skin cancer), abnormal blood pressure, heart disease, diabetes, an AIDS-defining illness, and uncorrected sensory deficits that would interfere with understanding the test instructions or performing the tests.

Use of psychoactive substances also was an exclusionary criteria. Respondents were questioned about their use of over-the-counter medications, prescriptive medications, recreational drugs, and alcohol. Respondents who used medications with psychoactive effects on an ongoing basis were excluded unless the medication was prescribed for treatment of HIV infection (e.g., AZT) and was obtained from a licensed source. Respondents were excluded if their alcohol use was greater than a predetermined level. Respondents reporting use of marijuana, stimulants, tranquilizers, sleeping medications, amyl nitrates, or steroids with a frequency greater than once per week were also excluded.

Each subject underwent a complete medical history, physical examination, and neurological examination. A complete blood count and chemistry panel were performed as well as a urinalysis to determine compliance with alcohol and recreational drug use restrictions. Two days after the completion of the medical testing, the subjects completed the information processing battery and the neuropsychological battery. The information processing battery consisted of four tests that assessed sustained attention (vigilance), spatial memory (matrix), speed of information processing (Sternberg, 1969), and mental arithmetic operations (running difference). The neuropsychological battery consisted of two mood scales, one scale of self-reported memory functioning, six subtests of the Wechsler Adult Intelligence Scale-Revised, one test of premorbid functioning, and 12 other neuropsychological instruments.

After the data were collected, research at the Naval Medical Research Institute indicated that the standard method of administering the Merieux test, which was used in this study to classify the subjects, produced unreliable results. The unreliability of this measure called into question the subject classifications in general and the Stage

3 versus Stage 4 assignments in specific. Because the distinction between a subject at Walter Reed Stage 3 versus one at Stage 4 rests on the results of the Merieux test, the original design had to be discarded.

After consultation with physicians at the Naval Health Research Center, we decided to focus on comparisons between asymptomatic subjects and the controls. The subsequent analyses are based on comparisons of the homosexual control subjects (N = 29), the heterosexual control subjects (N = 28), and the asymptomatic HIV+ group (Walter Reed Stages 1 and 2) (N = 29).

To determine if cognitive impairments are apparent at the asymptomatic stage of infection, we first had to identify the appropriate control group for the statistical comparisons. The homosexual control group differed significantly from the heterosexual control on one of the mood subscales, 14 dependent measures from three of the neuropsychological tests, and four measures from two of the information processing tests.

The original purpose for including the heterosexual control group was to allow comparisons to data obtained from military personnel and to control for lifestyle variables, such as alcohol and drug use, that are prevalent among sexually active homosexual men at risk for HIV infection. These variables are difficult to measure directly, but they can significantly influence cognitive performance. Thus, without controlling for the influence of these variables and by looking only at a control group of HIV- heterosexual males, the cognitive changes associated with HIV in Walter Reed Stages 1 and 2 may be overestimated. Therefore, we selected the homosexual control group to control for possible lifestyle differences that could affect performance on the cognitive tests.

The control subjects performed significantly better than the asymptomatic subjects on two of 18 dependent measures pre-selected by the project neuropsychologist. Additionally, the control subjects unexpectedly were found to have significantly poorer performance on one of the 18 variables, which measured speed of information processing. No significant between-group differences were found on tests contained in the information processing battery.

One conclusion that may be drawn from this study is that few deficits in cognitive performance are apparent in asymptomatic individuals when the subjects are rigorously screened and carefully matched. However, because the homosexual group was performing in the mild-to-moderately impaired range on the speed of information processing test and scored significantly lower than the heterosexual group on several tests, the degree of impairment in the asymptomatic group may be underestimated. Too few significant between-group differences were found overall to draw any conclusions about the relative sensitivity of neuropsychological versus information processing tests.

Other Findings

The main experiment also produced some unanticipated findings. One surprising finding occurred on the vigilance task. Subjects typically emit either no false alarms

or one false alarm during the test. However, 61 subjects who were tested in the main experiment emitted more than four false alarms during the task. The project neuropsychologist compared the background information and the results from the neuropsychological tests for subjects who demonstrated a high false alarm rate to other subjects who showed normal false alarm rates. The results of these analyses are presented in Damos and Parker (1994). Briefly, high false alarm rates may indicate recreational drug use and its associated neurocognitive decrements.

A second surprising finding concerned performance on the matrix task. A number of subjects in all of the experimental groups showed extremely erratic learning curves and very poor performance. In some cases, the average reaction times were almost 10 times slower than those of college students who had participated in previous studies. The second and third studies were undertaken to replicate these results and provide baseline data for future research.

SECOND STUDY

As mentioned previously, the matrix task had been used in a number of previous studies, none of which had produced data comparable to those obtained in the main experiment. However, the main study differed from the previous studies in three major ways. First, all of the earlier studies had used either college student or student naval aviators. Second, in the majority of the previous studies, the subjects had been given monetary bonuses for good performance. In the remaining studies, those using naval personnel, no payment was given. Subjects participating in the main study were given a flat fee for completing the study; no bonuses were given. Additionally, only a handful of subjects in the main study were college students. Third, in the majority of previous studies, the matrix task had been either the only test or the main test used in the experiment. In the main study, the matrix task was one of 18 tests in the information and neuropsychological batteries. Carry-over effects, therefore, potentially could account for the unusual performance of some of the subjects. Thus, the performance differences observed in the main study could have been caused by several different factors.

The second study was designed to determine which, if any, of the three factors described above could account for the observed behavior. Only college students were enrolled. Two different bonus payment schemes were used. One was a flat fee similar to that used in the main study. The second was the fee plus bonuses for good performance that had been used in earlier work.

The second study began with two groups of 15 college students. Each group received one of the two payment schemes. Both groups completed the same initial screening forms as subjects in the main study. However, none of these subjects performed any of the information or neuropsychological tests that preceded the matrix task in the main study. If no subjects demonstrated the unusual performance seen in the main study, then a third group would have been added that was treated identically to the subjects in the main study in terms of the cognitive testing.

One subject in each group demonstrated the same unusual performance seen in the main study. Thus, the extremely slow reaction times seem in the main study were not caused exclusively by differences in the subject population, the payment scheme, or carry-over effects. The subjects demonstrating the unusual performance reported either recent closed-head injury (although hospitalization was not required) or very early use of recreational drugs.

THIRD STUDY

The results of the second study imply that the matrix task may be a sensitive measure of some central nervous system (CNS) insults. However, the matrix task is not an ideal clinical instrument for several reasons. First, the task is too difficult for many individuals with CNS insults. Thus, easier versions of the task had to be constructed. Second, no data had been collected on female subjects. Third, the task has not been rigorously validated as a test of spatial short-term memory.

The third study was designed to address some of these shortcomings. Two simplified versions of the matrix task were developed. Both of these required comparisons between pairs of stimuli rather than continuous comparisons between successively presented stimuli. In the easiest version of the task, stimuli were presented simultaneously, eliminating the need for short-term memory.

Women as well as men participated in this study. By including both sexes in the study, gender-related differences in performance could be identified. All of the subjects performed the two new versions of the task as well as the standard matrix task.

To provide better insight into nature of the matrix task, the study also varied the time between the subject's response and the next stimulus presentation (RSI). In all preceding studies, this value was between 20 and 60 ms (machine dependent). In the current study it varied from 60 ms to 4000 ms. By examining both speed and reaction time as a function of delay, we should be able to determine which memory systems contribute to performance.

This study currently is underway and is being supported in part by the Institute of Safety and Systems Management at the University of Southern California. The estimated completion date is April 1, 1995.

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PRODUCTS OF THIS CONTRACT

Journal Articles

Damos. D.L. & Parker, E.S. (1994). High false alarm rates on a vigilance task may indicate recreational drug use. *Journal of Clinical and Experimental Neuropsychology, 16,* 713-722.

Damos, D.L. & Parker, E.S. (under review). Methodological issues in the study of HIV+ individuals. *Applied Ergonomics*.

Damos, D.L., Levine, A.M., John, R.S., & Parker, E.S. (under review). Cognitive deficits in HIV infection. *Journal of Acquired Immune Deficiency Syndromes.*

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Damos, D.L., & John, R. (1992). Identifying early cognitive impairment caused by HIV. *Proceedings of the XX Conference of the Western European Association of Aviation Psychology.* Hamburg, GR: DLR, Department of Aviation and Space Psychology.

Technical Reports

Damos, D., John, R., Parker, E., & Levine, A. (1994). *Identifying the cognitive decrements caused by HIV.* Los Angeles, CA: University of Southern California, Institute of Safety and Systems Management.

Presentations

Damos, D.L. (1992, October). *Identifying early cognitive impairment caused by HIV.*

Paper presented at the XX Conference of the Western European Association of Aviation Psychology.

Parker, E. S. (1994, August). *Memory decrement in HIV-infected individuals.* Paper presented at the Third Practical Aspects of Memory Conference held at the University of Maryland, College Park, Maryland.